

## Local allergic rhinitis: Concept, pathophysiology, and management

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Local allergic rhinitis (LAR) is a localized nasal allergic response in the absence of systemic atopy characterized by local production of specific IgE (sIgE) antibodies, a T<sub>H</sub>2 pattern of mucosal cell infiltration during natural exposure to aeroallergens, and a positive nasal allergen provocation test response with release of inflammatory mediators (tryptase and eosinophil cationic protein). Although the prevalence remains to be established, a number of patients previously given a diagnosis of nonallergic rhinitis or idiopathic rhinitis are now being classified as having LAR. Culprit allergens responsible include house dust mite, grass and olive pollens, and many others. For the diagnosis of LAR, neither skin prick testing nor determination of the presence of serum sIgE antibodies is useful, and a nasal allergen provocation test is needed to identify the culprit allergen or allergens. In a certain proportion of cases, local sIgE can be detected, and conjunctivitis, asthma, or both can be associated. Whether patients with LAR will have systemic atopy in the future is a matter of debate. Further studies are needed for examine the prevalence of this phenomenon in different areas, to improve the diagnostic methods to better identify these patients, and to develop therapeutic approaches, including the use of immunotherapy. (*J Allergy Clin Immunol* 2012;■■■■:■■■-■■■.)

**Key words:** Allergic rhinitis, eosinophil cationic protein, entopy, local allergic rhinitis, local specific IgE, nasal polyps, nonallergic rhinitis, nasal allergen provocation test, tryptase

Since the first evidence reported by Huggins and Brostoff<sup>1</sup> in 1975, further research has supported the concept of local

### Abbreviations used

AR:	Allergic rhinitis
ECP:	Eosinophil cationic protein
FLC:	Free light chain
HDM:	House dust mite
IR:	Idiopathic rhinitis
LAR:	Local allergic rhinitis
NAPT:	Nasal allergen provocation test
NAPT-S:	Nasal allergen provocation test with a single aeroallergen
NAR:	Nonallergic rhinitis
NARES:	Nonallergic rhinitis with eosinophilia syndrome
SCIT:	Specific subcutaneous immunotherapy
sIgE:	Specific IgE
SPT:	Skin prick test

production of IgE antibodies in the nasal mucosa of patients with allergic rhinitis (AR)<sup>2-4</sup> and nonallergic rhinitis (NAR).<sup>5-9</sup> These findings have been furthered with the identification of local allergic rhinitis (LAR)<sup>1,5-9</sup> as a condition involving a localized nasal allergic response in the absence of systemic atopy; “entopy” was the first term used to describe this phenomenon.<sup>7</sup> This entity is characterized by the following: local production of sIgE antibodies,<sup>1,8,9</sup> a T<sub>H</sub>2 pattern of mucosal cell infiltration during natural exposure to aeroallergens,<sup>5,7-10</sup> and a positive response to nasal specific allergen provocation test (NAPT)<sup>6,8,9,11</sup> manifested by symptoms and increased levels of sIgE, tryptase, and eosinophil cationic protein (ECP) in nasal secretions.<sup>12,13</sup>

In this article the work carried out on LAR is presented and discussed, and controversies are highlighted. In addition, directions are proposed for future basic and clinical research.

### ETIOLOGIC CLASSIFICATION OF RHINITIS

From an etiologic point of view, noninfectious rhinitis has been traditionally classified as allergic and nonallergic, and the diagnosis has been based on the clinical history, skin prick test (SPT) responses, and serum sIgE levels to inhalant allergens.<sup>14</sup> However, evidence has recently suggested that this approach is incomplete because patients previously given a diagnosis of NAR or idiopathic rhinitis (IR) might actually be classified as having LAR.<sup>6-9,11-13</sup>

AR is the most common form of noninfectious rhinitis,<sup>14</sup> but NAR can also affect an important number of patients. However, the exact prevalence of NAR is unknown, and minimal work has been done to identify NAR phenotypes by using standardized methods.<sup>14</sup> NAR is a heterogeneous group of nasal conditions,

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some of which are associated with a particular trigger or cause, although in the majority of patients with NAR, the cause is unknown and the terms IR or vasomotor rhinitis are used to categorize these patients.<sup>14</sup> Nonallergic rhinitis with eosinophilia syndrome (NARES) is another subgroup of NAR that, because of its characteristic mucosal eosinophilia, is considered a separate nosologic entity. In contrast with IR, patients with NARES respond well to nasal corticosteroids,<sup>14</sup> but its exact cause remains unknown.

Patients with NAR have been regarded as nonallergic because they have negative SPT responses and absence of serum sIgE. However, over the past decade, several studies have shown that a considerable number of patients with negative SPT responses, negative intradermal skin test results, and lack of serum sIgE who would otherwise have been categorized as having NAR have nasal symptoms after NAPT with a common aeroallergen, including house dust mite (HDM), grass and olive pollen,<sup>8,9</sup> and possibly others. Furthermore, recent studies suggest that local production of sIgE occurs in these patients.<sup>8,9,12,13</sup> As a result, the term LAR has been proposed,<sup>9</sup> leading to a new etiologic classification of rhinitis (Table I).<sup>14,15</sup> After the description of LAR in patients with a previous diagnosis of NAR, further studies are needed to define the clinical and immunologic differences between IR-NARES and LAR.

## EPIDEMIOLOGIC, CLINICAL, AND PATHOPHYSIOLOGIC ASPECTS OF LAR

The identification of a subgroup of patients who could be characterized as having LAR has generated a number of important questions:

1. What are the prevalence and overall effect of LAR, and what is the influence of environmental factors on the epidemiology of this condition?
2. Are the allergens associated with LAR the same as those involved in conventional AR?
3. How definitive is the evidence that IgE is produced locally in the nasal mucosa?
4. Is IgE production limited to the nose and why?
5. Is LAR a precursor or an end stage of systemic atopy, or does it represent a distinct entity with an independent natural history?
6. Is optimal LAR management identical to that of conventional AR?

A significant research effort will be required over the coming years to address all of these questions. Nevertheless, recent work has begun rendering information that will be presented below.

### Prevalence and effect

Although true prevalence data are not available, results generated in various European centers suggest that among patients with negative SPT responses and undetectable sIgE antibodies in serum, LAR might be present in 47% to 62.5% of patients with perennial<sup>6,8</sup> and seasonal<sup>9,11</sup> symptoms. Many of these patients were given a diagnosis of IR or NARES previously. These data indicate that LAR might be a common, although underestimated, entity.

Large studies in adults and children using consensus procedures for NAPT, nasal secretion collection, and laboratory

**TABLE I.** Etiologic classification of rhinitis

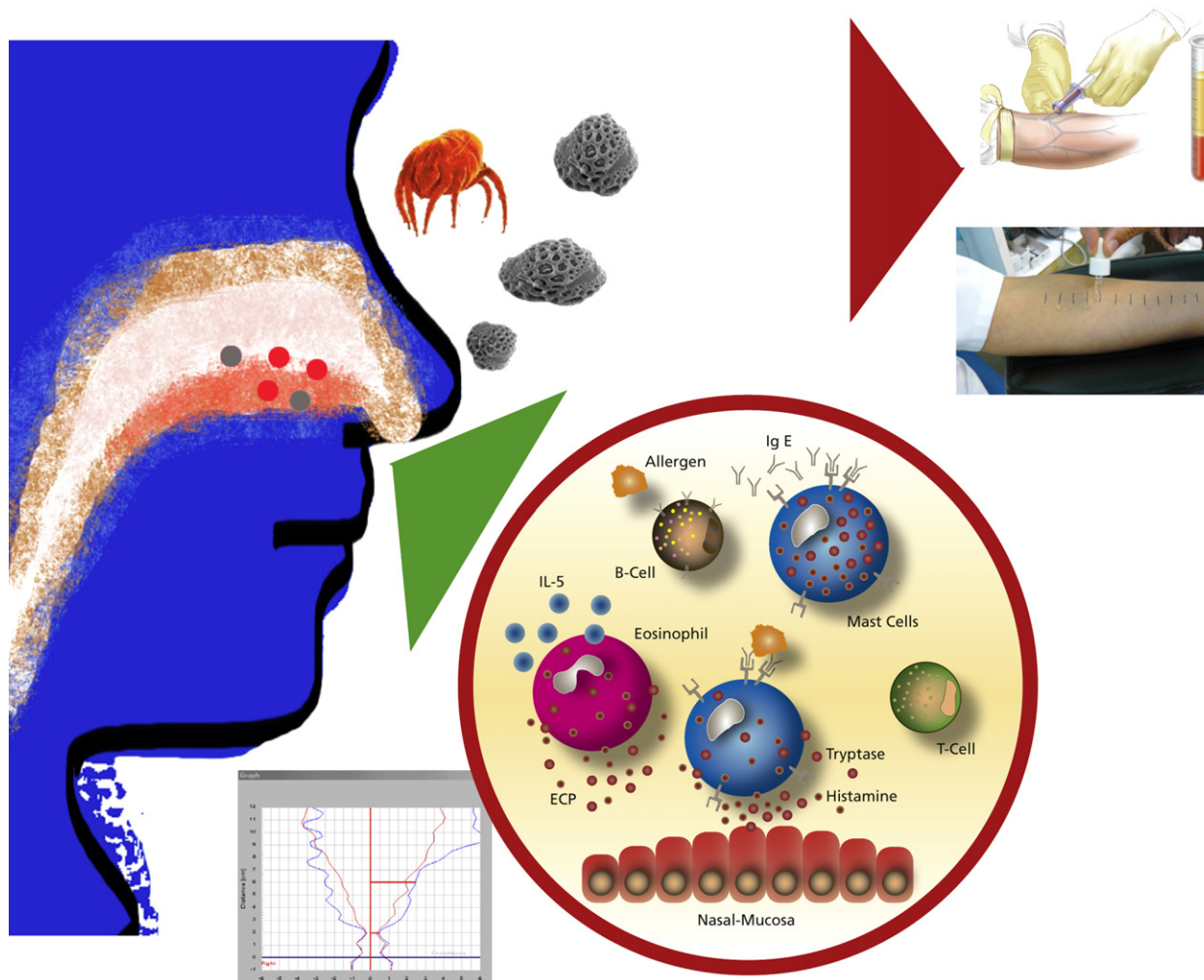
1. Allergic rhinitis
• Allergic rhinitis (with systemic atopy)
i. Classical classification
1. Time of exposure to aeroallergen or aeroallergens: perennial, seasonal, and occupational
ii. ARIA classification <sup>14</sup>
1. Duration of symptoms: persistent and intermittent
2. Severity of symptoms: mild, moderate, and severe
• Local allergic rhinitis (without systemic atopy)
i. Classical classification
1. Time of exposure to aeroallergen or aeroallergens: perennial, seasonal, and occupational
ii. ARIA classification <sup>14</sup>
1. Duration of symptoms: persistent and intermittent
2. Severity of symptoms: mild, moderate, and severe
2. Nonallergic rhinitis
• Infectious
• Occupational (irritant)
• Drug induced
• Hormonal
• Irritant
• Food
• Emotional
• Atrophic
• NARES
• Idiopathic

Adapted from Rondón et al.<sup>15</sup>

analytic techniques are needed to determine the epidemiologic characteristics of LAR. These studies should also define in more detail whether LAR has 1 or more unique clinical phenotypes, including comorbidities, which can distinguish it from other forms of nasal disease. For example, is it possible that LAR represents a relatively mild condition that responds well to pharmacologic rhinitis treatment leading to a diminished prevalence in specialty clinic populations, or is the opposite true?

An important consideration in assessing the prevalence of LAR is the influence of the environmental allergen load. Is this entity more frequent in some areas because of different levels of aeroallergen exposure? Also, are other environmental cofactors (eg, air pollution, temperature, and humidity) influencing the development of LAR as opposed to conventional AR? Answers to these questions require multicenter epidemiologic studies in geographic areas with a different environmental allergen load and varying atmospheric conditions.

Information published thus far has identified a few highly prevalent allergens as LAR culprits. These have primarily included HDM, grass, and olive pollen.<sup>1,6,8,9,11-13</sup> However, it is not yet known whether other common allergens or less frequent or unusual allergens are also involved. Other allergens to be considered include molds, animal dander, occupational allergens, and possibly others. Interestingly, in an article by Carney et al,<sup>6</sup> of 13 patients with presumed LAR, only 1 responded to nasal provocation with a dog/cat allergenic extract mixture. Substantial methodological difficulties will have to be surpassed to provide an adequate answer to this question. These include the determination of optimal allergen doses for NAPT and the development of more practical methods to conduct nasal allergen challenges. As will be discussed below, some progress toward solving the latter problem has been made.



**FIG 1.** Effect of allergen in the nasal mucosa produces a local IgE response with a  $T_H2$  inflammatory pattern with a reduction in nasal airway volume after allergen challenge (green arrowhead) but a negative skin test response and absence of IgE antibody in peripheral blood (red arrowhead).

## Pathophysiology

A characterization of pathophysiologic mechanisms (endotypes) and clinical manifestations (phenotypes) is needed for a better understanding of LAR. As stated above, the pathophysiology is described in more detail below (Fig 1).

**Local production of sIgE and inflammatory mediators in patients with AR and NAR.** Several authors have studied the concept of local production of IgE in nasal mucosa of patients with AR. Platt-Mills<sup>2</sup> showed increased levels of rye grass sIgE in nasal secretions of patients with AR, Durham et al<sup>3</sup> found expression of  $\epsilon$  germline gene transcripts and mRNA for the  $\epsilon$  heavy chain of IgE in nasal B cells, and further research has demonstrated the existence of class-switch recombination to IgE in nasal mucosa of patients with AR.<sup>4</sup>

After the detection of nasal sIgE in patients with NAR,<sup>1</sup> the presence of nasal sIgE in patients with LAR with perennial and seasonal symptoms during natural exposure to aeroallergens in as many as 22% in the former cases and 35% in the latter cases was demonstrated by Rondón et al.<sup>8,9</sup> The possible reasons for not detecting sIgE in a high proportion of patients with LAR with a positive NAPT response might be the low sensitivity of

the determination assays used by the dilutional effect of nasal lavage; the lack of inclusion of occult allergen or allergens; the existence of another immunologic mechanism, such as the possibility of nonspecific protease activity stimulation of HDM on airway innate immune cell; and others. The development of a noninvasive *in vitro* diagnostic technique with high sensitivity in detecting nasal sIgE would be a breakthrough in the diagnosis and screening of LAR.

More evidence supporting the local synthesis of sIgE in the nasal mucosa of patients with NAR has recently been reported,<sup>16</sup> although no studies have yet been carried out in patients with LAR. Powe et al<sup>16</sup> have demonstrated the localization of free light chains (FLCs) in tissue and nasal secretions of patients with AR and patients with NAR and proposed that they could function to mediate hypersensitive immune responses involving mast cells. Further investigation is needed to establish whether FLCs have an adjuvant or independent role in patients with IgE-mediated allergy and to elucidate the presence of FLCs in patients with LAR.

**$T_H2$  nasal inflammatory pattern.** Although the cause of IR is unknown, several pathophysiologic mechanisms have been

**TABLE II.** Presence versus absence of a T<sub>H</sub>2 inflammatory pattern in nasal mucosa of patients with NAR

Study	Study group	IR exclusion criteria	NAPT	Specimen	Laboratory techniques	Inflammatory cells (patients vs HC)
Blom et al <sup>17</sup>	40 persistent IR 10 HC	SPT (+), serum sIgE (+) CRS, NP, smoking	ND	Nasal biopsy and nasal brush	Immunohistochemistry	No difference in MC, EO, and IgE <sup>+</sup> cells
Powe et al <sup>5</sup>	17 IR 11 PAR 9 HC	SPT (+), CRS, NP, vasomotor rhinitis, asthma, or eczema	ND	Whole nasal turbinate	Immunohistochemistry and <i>in situ</i> hybridization	IR: ↑MC, EO, IgE <sup>+</sup> cells, T cells PAR: ↑MC, EO, IgE <sup>+</sup> cells, T cells, B cells
Powe et al <sup>10</sup>	22 persistent IR 21 PAR 19 HC	SPT (+), serum sIgE (+), CRS, NP, vasomotor rhinitis, asthma, or eczema	ND	Whole nasal turbinate	Immunohistochemistry	IR: ↑CD3 <sup>+</sup> , CD45RA <sup>+</sup> , CD25 <sup>+</sup> , CD8 <sup>+</sup> T cells PAR: ↑CD3 <sup>+</sup> , CD45RA <sup>+</sup> , CD25 <sup>+</sup> , CD8 <sup>+</sup> T cells, and APCs
van Rijswijk et al <sup>18</sup>	65 persistent IR 20 HC	SPT (+), serum sIgE (+) CRS, NP, smoking	ND	Nasal biopsy	Immunohistochemistry	No difference in lymphocytes, APCs, EO, macrophages, monocytes, MC, and other IgE <sup>+</sup> cells
Rondón et al <sup>8</sup>	50 persistent IR 27 LAR* 30 PAR 30 HC	SPT (+), serum sIgE (+), CRS, NP, vasomotor rhinitis	Yes	Nasal lavage	Flow cytometry	IR: ↑EO, CD3 <sup>+</sup> T cells LAR*: ↑EO, CD3 <sup>+</sup> , CD4 <sup>+</sup> T cells PAR: ↑EO, CD3 <sup>+</sup> , CD4 <sup>+</sup> T cells
Rondón et al <sup>9</sup>	12 seasonal IR 20 seasonal LAR 35 SAR 50 HC	SPT (+), serum sIgE (+), CRS, NP, vasomotor rhinitis	Yes	Nasal lavage	Flow cytometry	IR: ↑CD45 <sup>+</sup> , EO LAR: ↑CD45 <sup>+</sup> , EO, B-MC, CD3 <sup>+</sup> , CD4 <sup>+</sup> T cells SAR: ↑CD45 <sup>+</sup> , EO, B-MC, CD3 <sup>+</sup> , CD8 <sup>+</sup> T cells

APCs, Antigen-presenting cells; B, basophils; CRS, chronic rhinosinusitis; EO, eosinophils; HC, healthy control subjects; MC, mast cells; ND, not done; NP, nasal polyps; PAR, perennial allergic rhinitis.

\*IR subgroup with a positive NAPT response or positive nasal sIgE level.

proposed, including inflammatory and neurogenic mechanisms and changes in mucosal permeability.<sup>14</sup> The importance of an inflammatory mechanism in patients with NAR has been controversial in the past. Although several histologic and *in situ* hybridization studies found a T<sub>H</sub>2 inflammatory pattern with increased numbers of mast cells, eosinophils, IgE<sup>+</sup> B cells,<sup>5</sup> and T cells,<sup>10</sup> other studies found no significant differences between patients with NAR and control subjects.<sup>17,18</sup> These apparent contradictory results might be explained by the heterogeneity of NAR and the recent diagnosis of LAR in nonatopic subjects. These early studies included patients with a different pathogenesis, predominantly inflammatory in patients with NARES and possibly in patients with LAR,<sup>5,10</sup> and neurogenic mechanisms in patients with IR or vasomotor rhinitis (Table II).<sup>5,8-10,17,18</sup>

Recently, the existence of a nasal T<sub>H</sub>2 IgE-mediated inflammatory response has been confirmed in patients with LAR (Table II).<sup>8,9</sup> Flow cytometric studies in nasal lavage fluid demonstrated that patients with LAR and those with AR had a similar leukocyte-lymphocyte phenotype with increased levels of eosinophils, basophils, mast cells, CD3<sup>+</sup> T cells, and CD4<sup>+</sup> T cells during natural exposure to aeroallergens.<sup>8,9</sup> Moreover, more than 70% of patients with NAR and LAR presented criteria for NARES (nasal eosinophils >20%). Previously, Powe et al<sup>10</sup> found an increase in CD8<sup>+</sup> rather than CD4<sup>+</sup> T-cell numbers both in patients with NAR and patients with AR compared with numbers seen in control subjects and reduced numbers of antigen-presenting cells

in patients with IR compared with those seen in patients with AR (Table II). In this study sIgE antibodies were not determined, and furthermore, no NAPT were performed. Therefore the number of patients with LAR and their pathophysiologic characteristics were not evaluated.

**Positive NAPT responses.** Several studies have demonstrated that more than 47% of patients given a previous diagnosis of IR had LAR with positive NAPT responses monitored based on subjective (symptoms) plus objective parameters (acoustic rhinometry,<sup>8,9,11-13</sup> anterior rhinomanometry,<sup>6</sup> and nasal secretion of sIgE and inflammatory mediators<sup>12,13</sup>). The main characteristics of these studies are shown in Table III.<sup>6,8,9,11-13</sup>

The first kinetics study of local production of sIgE and inflammatory mediators after an NAPT was performed in patients with LAR sensitized to grass pollen.<sup>12</sup> The results showed that activation of mast cells and eosinophils and IgE production were induced after nasal stimulation with aeroallergens. Patients had an immediate or dual response to NAPT accompanied by release of tryptase, ECP, and sIgE in nasal secretions. The kinetics study of tryptase showed a strong correlation with nasal itching and sneezing and a pattern of release that varied with the type of response. Immediate responders presented with significantly higher levels of tryptase at 15 minutes and 1 hour after challenge compared with baseline values, whereas dual responders showed significantly increased levels from 15 minutes to 6 hours.<sup>12</sup> López et al<sup>13</sup> confirmed these results in patients with perennial LAR



**TABLE III.** Studies reporting positive NAPT responses in nonatopic patients with rhinitis

Study	Study groups	Saline challenge	Allergen concentration	Allergen volume per nostril	Positive NAPT response	Type of NAPT response	Evaluation of NAPT response	Reproducibility in repeated NAPTs
Carney et al <sup>6</sup>	23 persistent IR 8 PER 8 HC	Yes	DP/DF: 1+99 wt/vol Cats/dogs: 1+99 wt/vol Grass: 1+99 wt/vol	100 µL	13/21 (62%) 48% DP/DF 5% cats/dogs 5% grass 5% DP/DF + grass 8/8 (100%) 0/8 (0%)	100% ImR; LR was not evaluated	AAR	ND
Wedbäck et al <sup>11</sup>	17 seasonal IR 20 SAR 13 persistent IR	Yes	Birch or timothy: 10 <sup>2</sup> -10 <sup>3</sup> -10 <sup>4</sup> -10 <sup>5</sup> SQ unit/mL and pollen grains	25 µL	7/15 (47%) 19/19 (100%) 5/13 (39%)	43% DR; 57% LR 53% ImR; 47% DR 20% DR; 80% LR	Symptoms score and AR	ND
Rondón et al <sup>8</sup>	50 persistent IR 30 PER 30 HC 20 SAR	Yes	Der p 1: 0.04-0.4-1-2-4 (µg/mL)	100 µL	27/50 (54%) 30/30 (100%) 0/30 (0%) 0/20 (0%)	63% ImR; 37% DR ND – –	VAS and AR	ND
Rondón et al <sup>9</sup>	32 seasonal IR 35 SAR 50 HC 30 PAR to DP	Yes	Grass: 0.001-0.01-0.05-0.1 (µg/mL) Olea: 0.006-0.06-0.3-6 (µg/mL)	100 µL	21/32 (66%) 50% grass 3% olea 13% grass + olea 35/35 (100%) 0/50 (0%) 0/30 (0%)	26% ImR; 74% DR 60% ImR; 40% DR ND – –	VAS and AR	ND
Rondón et al <sup>12</sup>	30 seasonal LAR 30 HC	Yes	Grass: 0.1 µg/mL	100 µL	22/22 (100%) 0/24 (0%)	30% ImR; 79% DR –	VAS, AR, nasal sIgE, tryptase, and ECP	100% 100%
López et al <sup>13</sup>	40 persistent LAR 50 HC	Yes	Der p 1: 4 µg/mL	100 µL	36/36 (100%) 0/49 (0%)	60% ImR; 40% DR –	VAS, AR, nasal sIgE, tryptase, and ECP	100% 100%

–, Negative response to NAPT; AAR, anterior active rhinomanometry; AR, acoustic rhinometry; HC, healthy control subjects; ImR, immediate response; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; DR, dual response; LR, late response; ND, not done; PER, persistent allergic rhinitis; SAR, seasonal allergic rhinitis; VAS, visual analog scale of symptoms.

with positive NAPT responses to *Dermatophagoides pteronyssinus* (Table III). An important finding in both studies was the detection of a progressive increase in the levels of nasal sIgE from 1 to 24 hours after an NAPT.<sup>12,13</sup> This rapid secretion of sIgE after challenge, with basal detection of sIgE in some patients, supports the existence of a persistent local production of sIgE in nasal mucosa that rapidly increases after allergen stimulation.

All these findings have led researchers to consider the need to evaluate whether local production of sIgE in patients with other apparently nonallergic respiratory diseases, such as chronic rhinosinusitis with or without nasal polyps,<sup>19,20</sup> asthma,<sup>21-23</sup> or conjunctivitis, could exist.

### Local IgE production associated with nasal polyps

Nasal polyposis is a chronic inflammatory process of the nasal and sinus mucosa of unknown cause. In the last years, research has demonstrated that *Staphylococcus aureus* might modify airway disease by inducing synthesis of polyclonal IgE antibodies against superantigen from *S aureus*<sup>19</sup> and environmental allergens<sup>20</sup> in nasal polyp tissue.

This polyclonal mucosal production of IgE against several antigens (aeroallergens or not) constitutes a model of local IgE synthesis different from LAR, in which the specific antibodies to aeroallergens are correlated with the allergic clinical response and specific activation of B cells, mast cells, and eosinophils and are

commonly associated with low total nasal IgE levels. However, the clinical relevance of these findings needs to be established.

### Local IgE production associated with asthma

Evidence suggests an overlap between atopic and nonatopic asthma. Increased numbers of B cells undergo IgE heavy chain class-switch recombination,<sup>21</sup> with an increase in *IL4* and *IL5* mRNA expression in lung tissue from both atopic and nonatopic asthmatic patients.<sup>22</sup>

These findings have led to the following important questions: Is there an equivalent of LAR in patients with asthma, conjunctivitis, or both? Do patients with asthma also produce local IgE antibodies and a bronchial allergic response in the absence of systemic atopy? A recent work by Campo et al<sup>23</sup> described the existence of a positive response to bronchial challenge with *D pteronyssinus* with increased numbers of eosinophils and basophils in induced sputum in nonatopic asthmatic patients, warranting further studies.

## CLINICAL MANIFESTATIONS

### Nasal symptoms and comorbidities

Patients with LAR often present with symptoms typical of AR (ie, rhinorrhea, obstruction, sneezing, and itching), which are often associated with ocular symptoms, and good response to oral

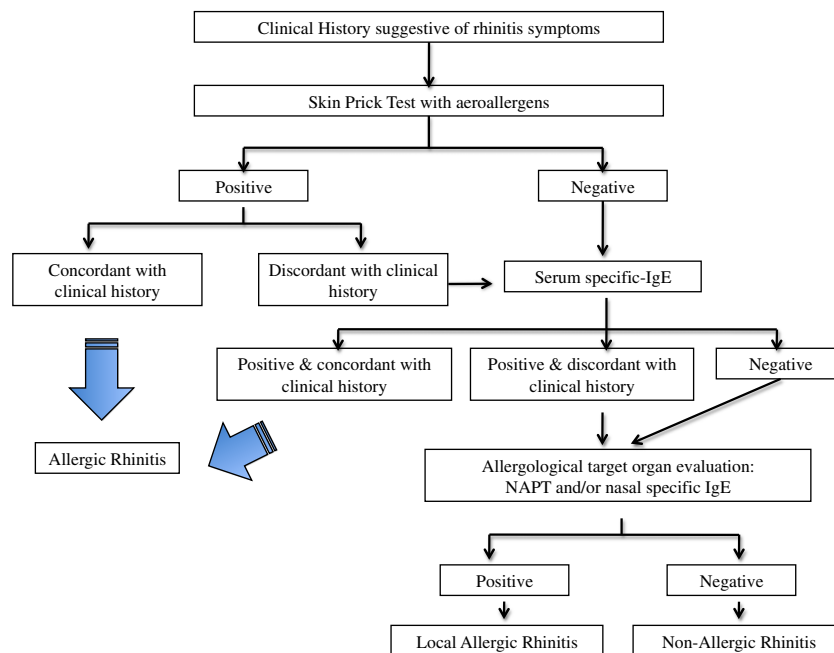


FIG 2. Diagnostic approach in patients with LAR. Adapted from Rondón et al.<sup>15</sup>

antihistamines and nasal corticosteroids.<sup>8,9,12</sup> Patients with LAR and systemic AR report anterior rhinorrhea, sneezing, and itching as the most frequent symptoms.<sup>8,9</sup> Patients with LAR can be grouped according to the classical (seasonal, perennial, and occupational) and Allergic Rhinitis and its Impact on Asthma (intermittent and persistent) classifications<sup>14</sup> at the same time because they do not overlap (Table I). The former is based on time of exposure to allergens, whereas the latter is based on persistence of symptoms.<sup>14</sup> The majority of patients with LAR studied reported persistent rhinitis with moderate-to-severe symptoms<sup>24</sup> frequently associated with conjunctivitis (25% to 57%) and asthma (33% to 47%).<sup>8,9</sup> No data have yet been published for LAR in children. Large epidemiologic studies (in adults and children) are needed to define the prevalence, severity, comorbidities, aeroallergens implicated, and clinical effects of LAR.

### Rethinking the atopic march

Given that LAR occurs rather late in life in a very high proportion of patients who do not report any symptoms indicative of allergy, questions remain as to whether these subjects are genuinely atopic.

Furthermore, of a large group of patients with NAR with negative SPT responses and serum sIgE levels, results in only 24% converted to positive (positive SPT responses, serum sIgE levels, or both), indicating that many subjects continue to have negative results.<sup>25</sup> In this context the concept of atopy must surely be broadened. If patients with LAR have AR over time, this supports the atopic march. For this purpose, in the case of LAR, the association with asthma, conjunctivitis, or both needs to be evaluated in more detail, and prospective studies involving large cohorts of patients are needed. One observation that would help clarify the atopic march is the study of LAR's evolution during a course of immunotherapy. Studies in progress indicate that patients with LAR undergoing immunotherapy with grass pollen

have skin test results that convert from negative to positive and have serum sIgE antibodies in spite of clinical improvement, as occurs with classical AR.<sup>24</sup>

### DIAGNOSTIC APPROACH

Several nonallergic conditions can mimic AR symptoms, but because management differs in each case, it is very important to differentiate between AR and NAR. Knowledge of the existence of a localized allergic response in the nasal mucosa demonstrates the need for a thorough allergologic workup. Rondón et al<sup>15</sup> have proposed a new diagnostic approach with a nasal allergologic evaluation in all patients with a clinical history suggestive of AR but with negative SPT responses and a lack of sIgE antibodies or in those whose clinical history is not concordant (Fig 2).

Diagnosis of LAR can be confirmed based on the detection of nasal sIgE, a positive NAPT response, or both in the absence of systemic atopy. Nasal lavage is a noninvasive method for the study of cells, inflammatory mediators, and other immunologic markers. Determination of sIgE levels in nasal lavage fluid has proved useful for detecting local sensitization both during natural exposure and after NAPT. This *in vitro* test has a high specificity but a low sensitivity of 22% to 40%<sup>8,9</sup>; whether the dilution effect, a nonspecific response to HDM, other factors, or both, might contribute to this low sensitivity must be evaluated. A nasal allergen provocation test with a single aeroallergen (NAPT-S) is a very useful diagnostic tool in patients with LAR,<sup>6,8,9,11</sup> with higher sensitivity than determination of nasal sIgE, tryptase, or ECP levels.<sup>8,9,12,13</sup> However, it is a very time-consuming technique, and its use might be limited in daily clinical practice. For this purpose, a new protocol of NAPT with multiple aeroallergens in one session has proved to be useful, specific, sensitive, reproducible, and less time-consuming for the screening of patients with LAR. The sequential application of several aeroallergens in one session did not produce any irritant response and showed 100%

concordance with the gold standard NAPT-S, achieving 75% reduction in the total number of visits required for final diagnosis in the NAR group and 55% reduction in patients with LAR compared with NAPT-S results.<sup>26</sup>

## THERAPEUTIC OPTIONS

The correct differentiation between LAR and NAR is a key point for the management of this new entity. The management of AR includes the following: allergen avoidance, pharmacologic treatment, immunotherapy, and education.<sup>14</sup> Patients with LAR have reported a good response to topical nasal corticosteroids and oral antihistamines.<sup>8,9</sup> This might be one phenotypic characteristic of patients with LAR in contrast with those with nonatopic rhinitis. Double-blind, placebo-controlled clinical trials will be of interest to compare the effectiveness of pharmacologic treatment in patients with LAR and those with AR.

An important consideration is whether patients with LAR could benefit from specific treatment, such as immunotherapy. A pilot observational study has just been carried out by Rondón et al<sup>24</sup> in patients with LAR sensitized to grass pollen. Fifty percent of patients were treated with preseasonal grass specific subcutaneous immunotherapy (SCIT) for 6 months and rescue medication in the spring (SCIT group), and the other 50% of patients received rescue medication alone (control group). In this study SCIT with grass pollen increased tolerance to the aeroallergen and reduced symptoms and rescue medication in patients with LAR compared with those seen in the control group. These interesting results highlight the need to conduct phase II double-blind, placebo-controlled clinical trials to evaluate whether LAR might be considered a new indication for specific immunotherapy.

## FUTURE RESEARCH

Increasing evidence of a localized allergic response in nonatopic patients raises important questions about LAR, many of them outlined in this article: studies of prevalence and incidence in adults and children, influence of the allergenic load in the production of disease, lower airway and conjunctival involvement, effectiveness of pharmacologic treatment, and specific immunotherapy.

Concerning natural history, it is relevant to know whether these patients remain stable over long periods of time, their symptoms decrease, or their symptoms evolve to those of classical AR. The fact that many patients have a history of LAR of many years' evolution without progressing to systemic AR support the idea it can be an independent entity.

However, the possibility exists that local sensitization would be the primary event in any AR disease and can develop into systemic classical AR over time. This requires appropriate prospective studies.

The allergologic evaluation of the target organ proposed in this review is necessary for the diagnosis of this new entity in patients with a clinical history indicative of allergy and negative SPT responses and absence of sIgE in serum. Additional research should also address a more detailed characterization of the inflammatory response in patients with LAR by conducting comparative studies between patients with LAR and those with AR, assessment of the presence of a local allergic response in patients with occupational rhinitis with or without asthma, and

consideration of the feasibility of genetic studies in a large group of patients given a diagnosis of LAR comparing them with the systemic AR and NAR groups.

**Clinical implications: Patients with NAR might have local sIgE antibodies in the absence of systemic sIgE. In suggestive cases with negative conventional test results, local nasal allergen provocation should be considered.**

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